Mitochondrial disturbances, tryptophan metabolites and neurodegeneration: medicinal chemistry aspects

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Running Title: Mitochondrial dysfunction and kynurenines in neurodegeneration

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Abstract: Neurodegenerative disorders, *e.g.* Parkinson's, Huntington's and Alzheimer's diseases are distinct clinical and pathological entities sharing a number of leading features in their underlying processes. These common features involve the disturbances in the normal functioning of the mitochondria and the alterations in the delicate balance of tryptophan metabolism. The development of agents capable of halting the progression of these diseases is in the limelight of neuroscience research. This review highlights the role of mitochondria in the development of neurodegenerative processes with special focus on the involvement of neuroactive kynurenines both as pathological agents and potential targets and tools for future therapeutic approaches by providing a comprehensive summary of the main streams of rational drug design and giving an insight into present clinical achievements.

Key words: clinical trials, drug discovery, excitotoxicity, kynurenic acid, kynurenine system, mitochondria, neurodegeneration, neuroprotection, quinolic acid, tryptophan metabolism.

INTRODUCTION

Neurodegeneration is characterized by progressive injury and loss of neurons in certain brain regions. The loss of function of these regions results in the development of distinct syndromes, *e.g.* Parkinson's, Huntington's and Alzheimer's diseases. These disorders are different clinical, biochemical and histopathological entities; however, they share some main common characteristics such as mitochondrial dysfunction, excitotoxicity, impaired antioxidant capacity and disturbances in tryptophan metabolism. The presence of either inherited or sporadic mutations as well as chronic exposure to certain environmental factors can all contribute to the complex etiology of neurodegenerative disorders. The beginning of the pathological processes precedes the onset of clinical symptoms by years or even decades, thus, the possible approaches to protect neurons from progressive degeneration and cell death are in the focus of research in neuroscience with promising results in the preclinical but rather disappointing ones in the clinical phases.

This review highlights the indisputable role of mitochondria in the development of neurodegenerative processes with special focus on the involvement of neuroactive kynurenines both as pathological agents and potential targets and tools for future therapeutic approaches.

MITOCHONDRIA

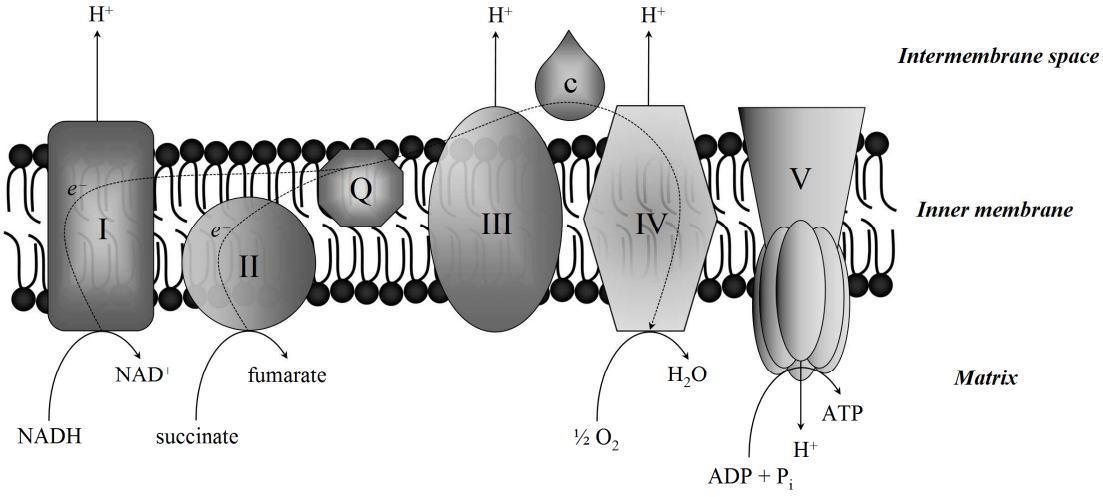
Mitochondrial structure and physiology

Mitochondria are membrane-bound elongated organelles in the cytoplasm supposed to evolutionary originate from the endosymbiosis of an ancient aerobic prokaryote from the Proteobacteria phylum into an early eukaryotic cell [1]. A mitochondrion comprises four distinct compartments. The porous outer membrane, which is freely permeable to ions and small molecules, contains important receptors and enzymes. The invaginated and convoluted inner membrane with cristae contains the enzymatic apparatus of the respiratory chain and

oxidative phosphorylation, some essential co-factors and carrier molecules. The inner membrane is enriched in cardiolipin and practically impermeable to small molecules and ions including protons. The intermembrane space is localized between the two membranes. The matrix is an aqueous medium encompassed by the inner membrane. It provides environment for several essential metabolic pathways such as the urea cycle, β-oxidation, pyruvate dehydrogenase complex, citric acid cycle (Krebs–Szent-Györgyi cycle), and contains structural proteins, enzymes and also its own genome, the mitochondrial DNA (mtDNA).

Mitochondria are responsible for several physiological cellular processes such as energy supply, thermogenesis, calcium homeostasis, regulation of cell-cycle, development and aging. Biologically utilizable energy is produced by the coupled function of the citric acid cycle (also known as tricarboxylic acid cycle) and the enzymatic complexes (complex I–V) embedded in the inner membrane (reviewed in [2]). Briefly, glucose and fatty acids are catabolized outside the mitochondria to form pyruvate and acyl-CoA, respectively. These compounds are then imported to the mitochondria and transformed to acetyl-CoA that subsequently undergoes oxidation within the citric acid cycle to favor the formation of reduced coenzyme NADH and succinate through multiple enzymatic steps. These compounds provide electrons for complex I, II respectively, within the respiratory complex chain. Complexes are functionally arranged in an electrochemical hierarchy according to their gradually increasing electronegativity and redox potential. The “downstream” flow of electrons provides energy for the pumping out of protons to the intermembrane space through complexes I, III and IV, the latter being responsible for the reduction of molecular respiratory oxygen to form H_2O in a process often referred as terminal oxidation. The export of protons from the matrix leads to the development of a proton gradient between the two compartments called mitochondrial membrane potential (negative inside) and an electrochemical gradient (alkaline inside). Since the inner membrane is impermeable to protons the electrochemical drive to equalize proton concentration can exclusively be achieved by the reentering of protons through F_1F_0-ATP synthase (complex V), the activation of which catalyzes the transformation of ADP into ATP in a process called oxidative phosphorylation [3]. ATP is a high-energy macromolecule that serves as the main energy source for eukaryotic cells. According to this chemiosmotic hypothesis mitochondria transform electrochemical energy into a biologically available form (Figure 1).

Figure 1. Schematic presentation of the function and organization of the mitochondrial respiratory chain



Complex I = NADH dehydrogenase; complex II = succinate dehydrogenase; Q = coenzyme Q10 (ubiquinone); complex III = ubiquinol-cytochrome *c* oxidoreductase; c = cytochrome *c*; complex IV = cytochrome *c* oxidase; complex V = ATP synthase.

Mitochondria possess their own genome in the matrix called mtDNA, which is a double-stranded circular DNA that is supposed to be in close relation to that of Rickettsiae. It contains 37 genes encoding 13 proteins, all of which are part of the respiratory complexes, 2 ribosomal RNAs and 22 transfer RNAs [4]. Any other mitochondrial function is carried out by proteins encoded by nuclear DNA (nDNA) and imported into the mitochondria. The mitochondrial genome is almost exclusively maternally inherited due to the ubiquitination and subsequent degradation of paternal mitochondria in the zygote [5]. It regularly replicates in postmitotic cells about once in a month in humans. Mitochondrial fission is a process in which mitochondria grow and divide in response to an increased energy demand. In addition, mitochondria are prone to constant fusion with each other resulting in the mixture (and possibly recombination) of normal and potentially mutated genomes (“heteroplasmy”). Approximately 2–15 copies of mtDNA are present in a mitochondrion (“polyplasmia”) [6]. During cell division mitochondria are distributed randomly into the daughter cells. These processes, on the one hand, can protect mitochondria and their host cells from the potentially deleterious effects of mtDNA mutations. On the other hand, they somewhat counterbalance the limited possibility of genomic recombination resulting from the uniparental inheritance.

Mitochondrial matrix can serve as a temporary buffering pool for intracellular Ca^{2+} storing it in the form of calcium phosphate, when the level of free Ca^{2+} in the cytosol increases beyond a certain set-point. After cytosolic Ca^{2+} level decreases below the set-point, Ca^{2+} is subsequently released from the mitochondria (reviewed in [7]).

There is a considerable amount of evidence indicating the regulating role of mitochondria in apoptosis and necrosis, the former being involved in the physiological processes of cell-differentiation and development (reviewed in [8]).

Mitochondrial pathophysiology, implications in excitotoxicity and neurodegeneration

During the process of terminal oxidation, the efficacy of the reduction of respiratory oxygen to H_2O is approximately 98–99%, while 1–2% of it is reduced incompletely to form superoxide anion ($O_2^{-\bullet}$), a moderately damaging but highly reactive free radical. Free radicals are molecules that possess unpaired electrons in their outer orbit making them extremely reactive towards organic macromolecules such as DNA, RNA, lipids and proteins via donating their unpaired electrons to the acceptor compounds in a process called oxidative damage. $O_2^{-\bullet}$ can be transformed into hydrogen peroxide (H_2O_2) both spontaneously and through a reaction catalyzed by manganese superoxide dismutase (MnSOD). H_2O_2 normally undergoes degradation by glutathione peroxidase and catalase enzymes. If H_2O_2 production exceeds the degradation capacity, it can react with transition metals (Cu^{2+} and Fe^{2+}) in the Fenton reaction to form a highly toxic hydroxyl radical ($OH^{-\bullet}$). $O_2^{-\bullet}$ is able to react with nitric oxide radical ($NO^{\bullet}$) to generate another highly toxic radical peroxinitrite anion ($ONOO^{-}$) in a reaction that is three times as fast as the dismutation catalyzed by MnSOD. These toxic radicals are often referred to as reactive oxygen species (ROS). The major source of ROS production in the cell is the mitochondrial electron transport chain; however, other relevant sources can also be mentioned such as NADPH oxidase, myeloperoxidase, xanthine oxidase, monoamine oxidase, cytochrome p450 and NOS (nitric oxide synthase).

Proteins that underwent nitrative/nitrosative or oxidative damage are particularly susceptible to rapid proteolytic cleavage and degradation. Damages to mitochondrial proteins can severely impair essential functions such as cell cycle regulation and ATP production (reviewed in [9]**)**. The damage to mitochondrial respiratory complex proteins by ROS results in the dysfunction of electron transport that leads to two main consequences. First, it results in the impairment of energy supply due to the decrease in ATP production. Second, it interferes with the efficacy of terminal oxidation, which in turn leads to enhanced ROS production and the generation of a vicious circle.

The damage to lipids caused by free radicals can interfere with normal membrane fluidity and may evoke the release of toxic by-products.

The mitochondrial genome is particularly sensitive to oxidative/nitrative/nitrosative injury due to several reasons [10]. It is in close vicinity to the main source of ROS production, it is not covered by protective histones, and it contains only few non-coding sequences. Because of these specific features, the mutation rate for mtDNA is approximately 10-fold higher than that for nDNA [11]. Defensive actions of mitochondria to counteract the production of ROS include a repair machinery entirely encoded by nDNA, an enzymatic apparatus to clear reactive species (*e.g.* SOD, catalase, peroxidase, peroxiredoxin) and low molecular weight antioxidants (reviewed in [12]). In addition, severely damaged mitochondria can be sensed, tagged and degraded in a process regulated by PINK1 and parkin genes [13,14]. It should be highlighted though that some mechanisms involved in mtDNA repair, *e.g.* the activation of poly(ADP-ribose) polymerase-1 (PARP-1) can also contribute to cell dysfunction and death by consuming NAD^+ and ATP *per se* [15]. The ability to cope with ROS-induced toxicity is thought to decline with aging [16], resulting in an increased rate of mtDNA point mutations and deletions in the somatic cells of the elderly [17].

The implications for the role of mitochondrial disturbances in neurodegenerative disorders come from a series of observations. First, the brain contains high amounts of polyunsaturated lipids that are extremely susceptible to ROS-induced lipid peroxidation; meanwhile, the neuronal antioxidant capacity is relatively low (reviewed in [18,19]). Second, the brain has an extreme energy demand accounting for 20% of total oxygen consumption, whereas it represents only 2% of the body mass [20]. In terms of this extremely high energy need, neurons show an absolute dependence on the constant availability of oxygen and glucose accompanied by a low capacity of glycogen storage, and a poor ability to increase glycolysis upon oxygen deprivation [21].

Glutamate is the major excitatory neurotransmitter in the human brain. The implications for a crucial role of elevated extracellular glutamate, and subsequent overactivation of ionotropic *N*-methyl-D-aspartate-sensitive glutamate receptors (NMDARs) in the etiopathology of neurodegenerative diseases are wide and thoroughly reviewed by others [22]. In the case of energy impairment, *e.g.* due to mitochondrial dysfunction, neurons exhibit partial membrane depolarization that can remove Mg^{2+} ions blocking the ionophore part of the NMDARs, allowing glutamate to evoke its downstream effects even in physiological concentrations [23]. The activation of NMDARs results in the influx of cations, predominantly Ca^{2+} into the cytosol. Among pathological conditions, intracellular Ca^{2+} level can be so high and permanent that it exceeds the buffering capacity provided by the mitochondrial Ca^{2+} sequestration, which in turn leads to the opening of high-conductance mitochondrial permeability transition pores (mtPTPs) [24]. It results in subsequent mitochondrial swelling, loss of mitochondrial membrane potential, impaired ATP and elevated ROS production (reviewed in [25]), and the release of apoptosis-inducing factor (AIF), procaspase-9 and cytochrome *c* from the intermembrane space into the cytoplasm, where cytochrome *c* takes part in the formation of apoptosomes composed by cytochrome *c*, caspase-9 and apoptotic protease activating factor 1 (Apaf-1) in a process ultimately leading to apoptosis [26]. In addition, elevated intramitochondrial Ca^{2+} levels can increase the activity of mitochondrial nitric oxide synthase (mtNOS) to produce highly toxic $NO^{\bullet}$ [27], which is known to impair the mitochondrial electron transport by competing with O_2 for the O_2-bindig site in complex IV [28]. Furthermore, it is capable of causing damage and cell death in multiple ways including the potential activation of the mtPTPs [29]. In this respect, NMDAR-mediated Ca^{2+} overload can lead to mitochondrial dysfunction, enhanced ROS production, energy crisis and eventually cell death, which can be either apoptotic or necrotic depending on the severity of the initial insult [30] and the subsequent mitochondrial dysfunction [31]. However, it has been proposed that not the Ca^{2+} overload itself, but the mechanism through which Ca^{2+} ions get into the cell could be the key-holder to NMDAR-mediated excitotoxicity [32]. Sattler et al. have demonstrated that NMDARs are spatially linked to neuronal nitric oxide synthase (nNOS) by a scaffolding protein PSD-95 (postsynaptic density protein of molecular weight 95 kDa) allowing Ca^{2+} ions to evoke the synthesis of $NO^{\bullet}$ in a toxic amount while entering into the cell upon NMDAR activation [33]. The possibly dominant role of nNOS in NMDAR-mediated excitotoxicity has also been supported by the results of earlier studies [34,35]. PSD-95 binds to the NR2B subunit of the NMDARs, which is fully consistent with the findings that glutamate excitotoxicity is principally mediated by NR2B subunit-containing NMDARs [36], which predominate in the extrasynaptic sites [37], where the

activation of these receptors has been proven to be neurotoxic (while synaptic NMDAR activation seems to be protective) [38,39].

The role of mitochondrial dysfunction and excitotoxicity in the process of neurodegeneration is clearly demonstrated (Figure 3). The development of agents being capable of intervening in the processes of mitochondrial dysfunction, particularly NMDAR-mediated excitotoxicity, is one of the key features in the attempts to treat or at least positively influence the course of neurodegenerative diseases.

THE KYNURENINE SYSTEM

Certain routes of the metabolism of the essential amino acid tryptophan (TRP) are widely known and have been extensively studied (*e.g.* serotonin pathway, melatonin pathway), whereas the main pathway of TRP metabolism has only been in the center of interest for the past 40 years. In fact, the kynurenine pathway is responsible for the catabolism of more than 95% of TRP in the brain through a multistep enzymatic process, which involves the production of niacin or nicotinic acid, providing the main component of NAD^+ and $NADP^+$ [40,41]. The central intermediate L-kynurenine (L-KYN) is produced via the rate-limiting step of TRP catabolism (for details, see Figure 2) and can be further metabolized through three distinct pathways resulting in the formation of anthranilic acid (ANA), 3-hydroxy-L-kynurenine (3-OH-L-KYN) and kynurenic acid (KYNA). The total L-KYN content in the mammalian brain is about 200 ng/g [42], 60% of which is produced in the periphery and taken up through the blood–brain barrier (BBB) [43,44] by a large neutral amino acid carrier [45]. The group of “neuroactive kynurenines” (reviewed in [46]) consists of the three neurophysiologically relevant metabolites: KYNA, 3-OH-L-KYN and quinolinic acid (QUIN), the latter is formed by the further enzymatic metabolization of 3-OH-L-KYN and ANA [47].

KYNA is formed via the irreversible transamination of L-KYN by kynurenine aminotransferase (KAT) enzymes, which have four known distinct subtypes in the mammalian brain (reviewed in [48]). KAT I seems to play a limited role in the human brain regarding KYNA production among physiological conditions [49]; however, it is suggested that the neuronal expression of KAT I is involved in the regulation of development and apoptosis [50]. KAT II is proven to be the main enzyme of KYNA production noth in the human and in the rat brain, whereas it has been demonstrated to have the lowest activity in mice, where the main KYNA producer is KAT IV, which was found to be identical with mitochondrial aspartate aminotransferase (mtAAT) [51]. KAT III shares a number of common features with KAT I, but it has not been demonstrated to have any activity in the human brain [52]. Functionally, KYNA is a broad-spectrum antagonist of excitatory amino acid receptors with high affinity towards the strychnine-insensitive glycine coagonist site of NMDARs [53]. Besides, KYNA exerts a weak antagonistic effect on kainate- and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-sensitive ionotropic glutamate receptors [54]. However, recent reports on the effect of KYNA on AMPA receptor-mediated responses revealed a dose-dependent dual action, which favors facilitation in low (nanomolar-micromolar [55], nanomolar [56]) concentrations, whilst neuroinhibition in high (millimolar [55], micromolar [56]) concentrations. KYNA also possesses a non-competitive inhibitory

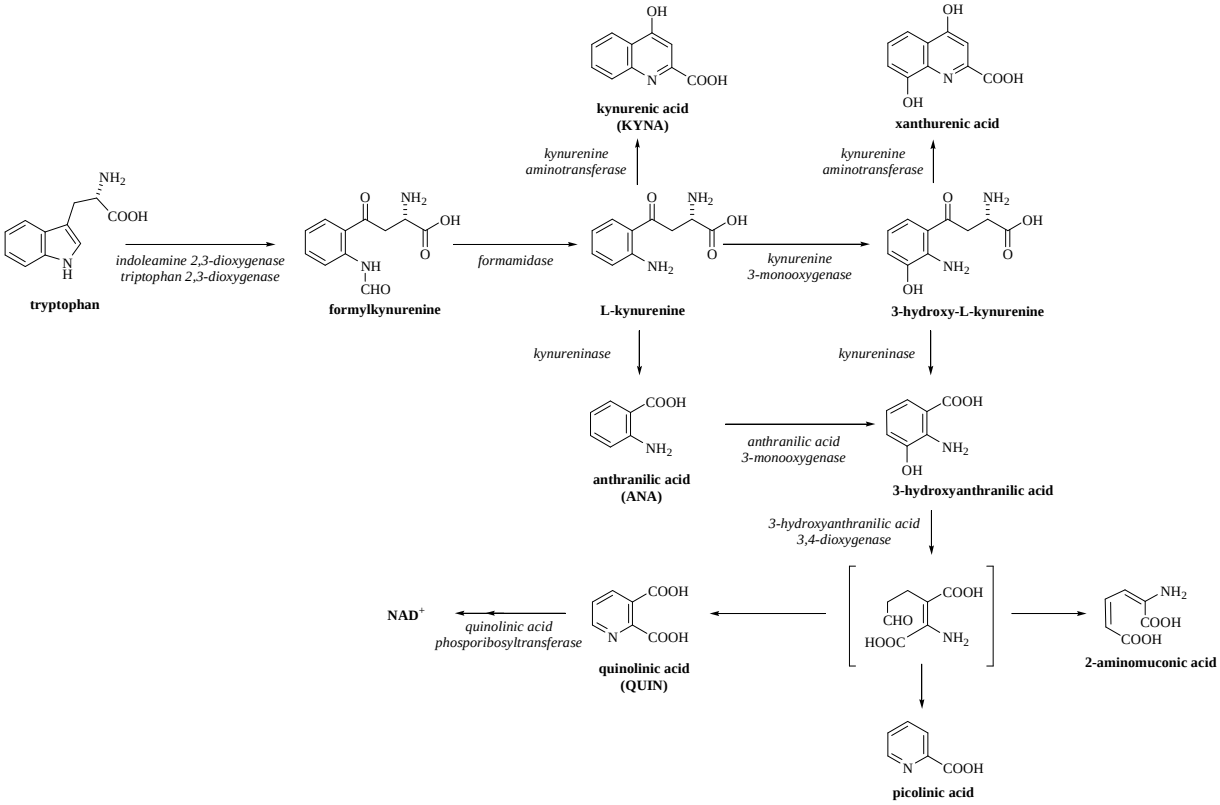
effect on α7 nicotinic acetylcholine receptors [57] through which KYNA is involved in the negative regulation of presynaptic glutamate release [58]. Moreover, KYNA increases the expression of non-α7 nicotinic acetylcholine receptors [57]. As a modulator of glutamate activity KYNA is proposed to be one of the endogenous neuroprotective agents (widely reviewed by Zadori et al. [59]). The dose-dependent neuroprotective efficacy of KYNA has been postulated and confirmed in a number of animal paradigms including kainate- [60,61], ibotenate- [61], QUIN- [61,62] and NMDA-induced neurotoxicity [61,63,64]. Furthermore, KYNA appears to possess a potent anticonvulsant effect even in physiological concentrations [65]. The effect of KYNA to block the activity of NMDARs is in accordance with the typical findings of behavioral studies subsequent to its intracerebroventricular administration in rats [66,67]. Additionally to its widely demonstrated anti-excitatory efficacy, KYNA has most recently been described as a potent free radical scavenger and antioxidant *in vitro* and *in vivo* [68].

QUIN is a specific, but rather weak and low-affinity competitive agonist of NMDARs that contain NR2A and NR2B subunits [69]. In contrast to KYNA, QUIN has proved to be neurotoxic in a number of animal paradigms and seem to exert its deteriorating effects on multiple ways including NMDAR activation [70], presynaptic glutamate release enhancement [71,72], astrocytic glutamate uptake inhibition [72], endogenous antioxidant depletion [73], ROS production [74] and lipid peroxidation [75]. The probable dominant role of NMDAR activation in QUIN-induced toxicity is supported by the findings that the activation of NOS enhances, its selective inhibition decreases [76], whereas the NMDAR blocker MK-801 completely abolishes lipid peroxidation induced by QUIN [77].

The detrimental effects of 3-OH-L-KYN have proven to be independent from NMDAR functioning but are rather due to its intracellular uptake and subsequent ROS production [78], and are at least partly mediated by its neurotoxic metabolite 3-OH-ANA, which is prone to undergo auto-oxidation in a process resulting in superoxide production [79]. The intrastriatal co-administration of 3-OH-L-KYN and QUIN in subtoxic doses revealed a synergistic effect of these compounds leading to a substantial loss of neurons, which provides evidence that the presence of 3-OH-L-KYN can increase the risk of neurodegeneration during excitotoxic insults if QUIN is involved in the process [80].

It is noteworthy to mention that the different types of glia cells preferentially express or quite conversely lack the expression of certain enzymes in the metabolic pathways. Astrocytes, the major producers of KYNA in the CNS, are known to lack kynurenine 3-monooxygenase (KMO, kynurenine 3-hydroxylase) in favor of the synthesis of KYNA, whereas microglial cells and macrophages exhibit low KAT enzyme expression, which offsets the balance of TRP metabolism towards the direction of QUIN. A paradox role of astrocytes is revealed when surrounded by microglial cells or macrophages that can produce toxic amounts of QUIN from L-KYN excessively generated by astrocytes [81]. These preferences may contribute to the higher resistance of astrocytes against excitotoxic and ROS-generating stimuli, and also to their involvement in neuroprotection. In addition to the recent findings that TRP metabolism and KYN pathway possess a key regulatory role in the processes of immune response and tolerance (reviewed in [82]), these data provide a deeper insight into the role of inflammation accompanied by microglial and macrophage infiltration in the pathogenesis of neurodegenerative disorders.

Figure 2. The metabolism of tryptophan



Due to the fact that KYNA itself poorly penetrates the BBB [45], and has a limited selectivity and affinity towards the glycine-binding site of the NMDARs [83], a number of pharmaceutical approaches have been established to exploit its therapeutic potential. These approaches include three mainstream strategies. The first is the synthesis of KYNA analogues and prodrugs (reviewed in [84]). The most frequent molecular modifications result in halogenated KYNA analogues (*e.g.* 7-Cl-KYNA [85]) and its BBB-penetrant prodrug 4-Cl-KYN [86,87]), thiokynurenates [88], sugar conjugates of KYNA or its analogues (*e.g.* D-galactose-7-Cl-KYNA, D-glucose-7-Cl-KYNA [89] and glucosamine-KYNA [90,91]) and most recently kynurenic acid amides [92-96] that are proposed to be selective inhibitors of NR2B subunit-containing NMDARs [97]. Halogenated and thio-substituted derivatives possess increased selectivity and affinity towards the glycine-binding site of NMDARs [98], whereas the conjugation with sugars increases the penetration through the BBB via "hitchinking" on sugar transporter molecules [89]. The second strategy represents the systemic administration of L-KYN, which is known to penetrate the BBB better. L-KYN either alone or in combination with probenecid (an inhibitor of transmembrane organic acid transport) has been proven to be neuroprotective [99-102] and anticonvulsive [103,104] serving as a non-selective precursor for astrocytic KYNA synthesis. The co-administration of probenecid is a widely applied technique to overcome the rapid clearance of L-KYN, kynurenic acid and its derivatives [105]. The third main approach is the specific modulation of enzyme activities involved in TRP metabolism towards the enhancement of protective KYNA synthesis and attenuation of the detrimental metabolites QUIN and 3-OH-L-KYN.

The three main targets of enzyme inhibitors are KMO, kynureninase and 3-hydroxyanthranic acid 3,4-dioxygenase (3-HAO). Nicotinylalanine was one of the first potent KMO inhibitors with a relatively small specificity [100,106,107]. The most widely used KMO inhibitors with enhanced specificity include (*m*-nitrobenzoyl)alanine [108], 4,5-dichlorobenzoylalanine (PNU 156561, formerly referred as FCE 288833A) [109], (1S,2S)-2-(3,4-dichlorobenzoyl)-cyclopropane-1-carboxylic acid (UPF 648) [110], 3,4-dimethoxy-[-N-4-(nitrophenyl)thiazol-2-yl]-benzenesulfonamide (Ro 61-8048) [111] and most recently its prodrug 2-(3,4-dimethoxybenzenesulfonylamino)-4-(3-nitrophenyl)-5-(piperidin-1-yl)methylthiazole (JM6) [112], which is presumed to overcome the rapid diminish of Ro 61-8048 from the circulation. The inhibition of kynureninase is achieved by structural analogues of its substrate L-KYN including (4R)- and (4S)-dihydro-L-KYNs [113], *S*-aryl-L-cystein *S*,*S*-dioxides [114], byciclic L-KYN analogues [115], phosphinic acid L-KYN analogues [116], (*o*-methoxybenzoyl)alanine [117] and desaminokynurenine derivatives [118]. Notably the KMO inhibitors nicotinylalanine and (*m*-nitrobenzoyl)alanine also affect the activity of kynureninase [119]. The third related enzyme 3-HAO can be inhibited by the structural analogues of 3-hydroxy-anthranilic acid (3-OH-ANA). The most widely studied derivatives are the 4-halogenated [120] and 4,6-dihalogenated 3-OH-ANAs, among which 4,6-dibromo-3-OH-ANA (NCR-631) has deserved a great attention for its potent neuroprotective, anti-inflammatory [121] and anticonvulsant [122] properties, especially since the applied dose has been shown to cause no alteration in brain QUIN and KYNA levels by the same research group [123]. Interestingly, (*o*-methoxybenzoyl)alanine, a selective kynureninase inhibitor can exert inhibition on 3-HAO as well, in a process depending on the presence of mitochondria [124]. The KYNA analogue prodrug 4-Cl-KYN is also able to exert potent inhibition on 3-HAO through its metabolite 4-Cl-3-OH-ANA [125]. Though the inhibition of these enzymes can influence the syntheses of both KYNA and QUIN, it has been implicated that the reduction of QUIN levels could be more important than the elevation of KYNA regarding their protective features [126].

Although they seem to be rather secondary to the underlying processes, the alterations in the delicate balance of TRP metabolism between the pathways towards KYNA and QUIN production can possess a crucial role in the development of certain neurodegenerative diseases. Selective manipulations of the kynurenine system might harbor valuable therapeutic potential.

PARKINSON'S DISEASE

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), the decrease of dopamine and its metabolites in the striatum and the presence of Lewy bodies [127]. Clinical symptoms include bradykinesia, rigidity, resting tremor and postural instability [128,129]. The development of Parkinson's disease has been associated with the complex interplay of environmental and genetic factors. We can distinguish between idiopathic/sporadic and familial PD. A number of genes have been associated with the development of familial PD (PARK genes) (reviewed in [130]), most of them having direct implications in mitochondrial dysfunction.

Mitochondrial dysfunction in PD

The involvement of mitochondrial dysfunction in the pathogenesis originates from the discovery of the synthetic drug side-product 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the administration of which has been found to almost perfectly recapitulate parkinsonian symptoms and pathology with the exception of Lewy body formation [131]. Accumulating within the mitochondria MPP+ (1-methyl-4-phenylpyridinium), the active metabolite of MPTP impairs the activity of complex I [132] selectively in the dopaminergic neurons of SNpc [133]. The inhibition of electron transport in these neurons has become the main animal model of PD. Besides MPTP intoxication, selective mitochondrial dysfunction can be achieved by known environmental pesticides such as the natural insecticide *rotenone,* the quaternary ammonium herbicide *paraquat,* and the manganese-containing dithiocarbamate fungicide *maneb,* which are capable of inhibiting complex I, I and III, respectively (widely reviewed in [134]). Human studies regarding the activity of electron transport complexes in platelets, muscle cells, SNpc and cortical neurons have provided contradictory findings. Although systemic complex I deficiency still seems to be a predominant feature in the development of PD [135], recent findings have questioned its primary role in the pathomechanism of PD-related toxins [136].

Epidemiological studies (reviewed in [137]) along with recent genome-wide single nucleotide polymorphism (SNP) analyses [138] have indicated that the development of idiopathic PD is rather due to environmental factors than mere genetic heritability; however, the presence of certain mtDNA and nDNA mutations has been associated with this form of the disease including the polymorphisms in mtDNA polymerase gamma 1 (POLG1) [139,140] and complex I subunit ND5 [141]. On the other hand mtDNA haplotypes J and K [142] and the haplotype cluster UKJT [143] have been reported to be protective for their carrier population.

The majority of gene mutations found to be causative in familial PD can be associated with mitochondrial dysfunction. The gain-of-function mutation of PARK1 leads to extensive mitochondrial accumulation of its product *α-synuclein* [144], the main constituent of Lewy body inclusions, leading to the inhibition of complex I *in vitro* [144], *in vivo* [145] and in post mortem human studies [144]. The interaction of α-synuclein with complex IV has also been demonstrated [146]. Its transgenic overexpression in mice results in increased vulnerability against mitochondrial neurotoxins paraquat and MPTP [147], whereas α-synuclein knock-out mice are resistant to MPTP and intriguingly to 3-nitropropionic acid (3NP) and malonate as well, which are mitochondrial toxins widely used in modeling Huntington's disease [148]. However, there seems to be a bidirectional relationship between mitochondrial dysfunction and α-synuclein since the impairment of mitochondrial function itself can lead to the formation of α-synuclein inclusion bodies [149]. The product of PARK2 gene *parkin* is involved in the polyubiquitin tagging of potentially dangerous and aggregation prone protein substrates for proteosomal degradation via its ubiquitin E3 ligase activity [150]. Its potential mitochondrial function includes the maintenance of physiological antioxidant status by the regulation of gluthatione metabolism [151] and SOD activity [152]. Parkin is suggested to be involved in mitochondrial replication and transcription as well, through a direct association with mitochondrial transcription factor A (TFAM) [153]. Its overexpression has demonstrated

the important role of parkin in mitochondria-dependent cell death via the inhibition of cytochrome *c* and caspase 3-mediated apoptosis [154], and has proven to be effective in rescuing mitochondrial dysfunction caused by PINK1 loss-of-function [155]. Animal knock-out models of parkin exhibit severe mitochondrial degeneration accompanied by the decreased expression of several subunits of complex I and IV [156,157], but, interestingly, no increase in the susceptibility against MPTP intoxication has been reported [158]. PARK6 encodes the phosphatase and tensin homologue (PTEN)-induced putative kinase 1 (*PINK1*). PINK1 loss-of-function exhibits similar features with that of parkin including the phenotype of mitochondrial degeneration [159], and the decrement in the activity of mitochondrial complexes [160]. It is suggested that PINK1 and parkin share a common mechanistic pathway with PINK1 acting upstream of parkin [161] in a number of mitochondrial processes including the regulation mitochondrial dynamics [13,14]. Contrary to parkin, the defect of PINK1 has recently been reported to increase the extent of toxicity in MPP+/MPTP paradigms [162]. PINK1 is able to prevent the release of cytochrome *c* and subsequent apoptosis via the phosphorylation of its substrate TRAP1 (tumor necrosis factor receptor-associated protein 1) *in vitro* [163]. The involvement of PINK1 in the regulation of cell death is further highlighted by the finding that mtPTPs can open up even due to physiological calcium stimuli in PINK1-deficient cells [164]. High temperature requirement factor A2 (*HtrA2* or *Omi*), the product of PARK13 gene also acts downstream of PINK1 in preventing mitochondrial dysfunction [165]. Omi has been demonstrated to serve as a mitochondrial protein quality controller and a regulator of autophagy [166]. Knock-out of PARK13 results in selective striatal neuronal loss and parkinsonian motor deficits in mice [165]. PARK7 protein *DJ-1* is suggested to be an oxidative stress sensor being capable of modulating mitochondrial transcription and glutathione metabolism during mitochondrial stress [167]. The loss of its function results in impaired ROS scavenging [168] and increased susceptibility to MPTP [169], paraquat and H_2O_2-induced mitochondrial toxicity [170]. Recently, DJ-1 has also been identified as a deregulator of astrocytic inflammatory processes [171]. DJ-1 seems to work in parallel with PINK1/parkin pathway to maintain mitochondrial function during oxidative environment [172]. Furthermore, a definite complex interplay has recently been suggested between these three PD-related proteins (called PPD complex) in the degradation of misfolded/unfolded proteins; however, this hypothesis warrants further investigations [173]. Apart from the knowledge that PARK8 protein leucine-rich repeat kinase 2 (*LRRK2)* has been found to co-localize with membrane bound intracellular structures including mitochondria [174], little has been known about its role in mitochondrial pathology until very recently. Human [175] and *in vivo* studies [176] indicate that the LRRK2 mutation G2019S, the most common mutation in both familial and sporadic PD is associated with impaired mitochondrial function and morphology [175] and an enhanced sensitivity to mitochondrial stressors [176].

A number of pre-clinically effective drug candidates against mitochondrial dysfunction in PD have already reached the clinical phases (widely reviewed by Klivenyi et al. [177]. The phase II safety-trial of *inosine* (SURE-PD), the BBB-penetrant precursor of the natural antioxidant uric acid, is on its way, based on the retrospective observation of two prior clinical studies (DATATOP [178], PERCEPT [179]) that high normal levels of serum uric acid provided marked suppression on the rate of clinical progression.

Coenzyme Q10 or *ubiquinone* is another potent antioxidant physiologically functioning as an electron acceptor that transfers electrons from complex I and II to complex III in the respiratory chain. After its efficiency has been proven in *in vitro* and *in vivo* models of parkinsonism [180-182], Q10 seems to slow disease progression in patients with early PD but not in midstage PD according to the results of the completed phase II [183] and phase III [184] clinical studies. A phase III trial (QE3) with larger doses is currently running; however, the recent negative findings with the mitochondria targeted quinone derivative MitoQ suggests little hope [185].

The neuroprotective efficacy of *creatine* via buffering energy deficit in mitochondrial dysfunction has been demonstrated in a number of neurodegenerative animal models (widely reviewed by Beal et al. [186]) including MPTP [187,188] and rotenone [189]; furthermore, its co-administration with coenzyme Q10 has provided an additive neuroprotection in chronic MPTP paradigm [190]. Creatine has already proved to be non-futile [191] and safe [192] in a phase II clinical trial (NINDS NET-PD) and has showed ~50% improvement in Unified Parkinson's Disease Rating Scale at one year. The phase III trial is currently ongoing (NET-PD LS-1).

Peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α (PGC-1α) possesses a key integratory role in the transcriptional control of cellular energy metabolism, mitochondrial function and biogenesis, and oxidative stress defense (reviewed in [193]). PGC-1α knock-out mice exhibit increased vulnerability against both MPTP and kainic acid treatment [194], whereas its overexpression protects neurons against mitochondrial dysfunction due to mutant α-synuclein [195] and rotenone [195]. Correspondingly, the underexpression of genes depending on the function of PGC-1α system has also been demonstrated in human patients with Parkinsons's disease in a very recent genome-wide meta-analysis [195], and an SNP study has revealed possible associations of PGC-1α polymorphisms with risk, age of onset and longevity in PD [196]. Pioglitazone, a widely known agonist of PPARγ enhances the activity and expression of PGC-1α [197], besides it exerts transcriptional repression on a range of inflammatory proteins (reviewed in [198]). It has already proved its efficacy MPTP studies [199,200] and the phase II safety and futility clinical trial is already recruiting its participants with early Parkinson's disease (NCT01280123).

SNpc neurons possess specific vulnerability against the engagement of L-type Ca(v)1.3 Ca^{2+} channels due to subsequent mitochondrial oxidative stress [201]. Blocking these channels by *isradipine* showed neuroprotective efficacy in animal models of PD [202,203] without impairing the autonomous pacemaking activity of SNpc neurons [204]. Moreover, isradipine has proven to be of therapeutic use against L-DOPA-induced dyskinesias [205]. A phase II clinical trial examining the safety and the efficacy of isradipine administration in PD patients has just been finished (NCT00753636), another one is currently active (STEADY-PD).

PD and the kynurenine system

Considering that SNpc receives glutamatergic inputs from a number of cortical and subcortical regions including the cerebral cortex, subthalamic nucleus and amygdala

(reviewed in [206]), and that complex I deficiency results in increased sensitivity to excitotoxic insults in SNpc of PD patients [135], furthermore, that the role of mitochondrial $NO^{\bullet}$ accumulation in PD has recently emerged (reviewed in [207]), it is understandable that an increasing interest is focusing on the potential roles of endogenous neurotoxins and neuroprotectants of the kynurenine system in the pathogenesis of the disease.

The systemic administration of MPTP has been demonstrated to decrease KAT I activity in murine SN [208], and *ex vivo* rat cerebral cortical slices show diminished activity of KAT II and subsequent decrease in KYNA following MPP+ insult [209]. Consistent human post mortem studies of PD brains have reported decreased KYNA level and L-KYN/3-OH-L-KYN ratio in the putamen, SNpc and the frontal cortex, and elevated 3-OH-L-KYN level in SNpc and the putamen [210]. Plasma levels of QUIN have also been found to be elevated in PD patients [211]. The switch of TRP metabolism to the direction of 3-OH-L-KYN and QUIN might be secondary to the inhibited state of complex I and subsequently increased NAD^{+} demand, and it may contribute to further nigrostriatal degeneration by enhanced excitotoxicity and oxidative stress.

Interestingly, there seems to be a physiological inverse regulation between striatal KYNA and dopamine levels. Systemic administration of L-DOPA [212] and D-amphetamine [213] causes a decrease in KYNA levels in the rat brain. On the other hand, exhibits indirect inhibition on dopamine release KYNA in nanomolar concentrations by blocking astrocytic α7 nicotinic acetylcholine receptors, whereas direct inhibition in higher concentrations through blocking NMDARs and non-NMDARs [214]. In addition, the selective inhibition of KAT II leads to a two- to threefold increase in extracellular striatal dopamine level, which can be rescued by the co-infusion of KYNA [215]. Thus, dopaminergic stimulation, *e.g.* by D-amphetamine or L-DOPA can theoretically and experimentally result in higher striatal vulnerability against excitotoxic insults further deteriorating nigrostriatal degeneration [216]. However, chronic admininistration of L-DOPA, which is the first-line symptomatic therapy in PD, has previously been demonstrated by others to have no deteriorating effect on the remaining nigrostriatal neurons [217].

The co-infusion of nicotinylalanine, L-KYN and probenecid into SNpc provides protection against neurotoxicity induced by locally administered NMDA and QUIN in rats [100]. Furthermore, the bilateral injection of KYNA to the medial segment of globus pallidus of severely parkinsonian MPTP-treated monkeys [218,219] and rats [219] alleviate motor symptoms such as akinesia, tremor and rigidity in a dose-dependent manner [219].

Taken together, the long-term pharmacological increase of brain KYNA levels might be beneficial in PD due to its neuroprotective potential; furthermore, it has been proven to be effective in treating L-DOPA-induced dyskinesias without compromising the antiparkinsonian effect of chronic L-DOPA therapy in monkeys [220].

HUNTINGTON'S DISEASE

Huntington's disease (HD) is a chronic inherited autosomal dominant neurodegenerative disorder characterized by the preferential loss of the striatal γ-aminobutyric acidergic (GABAergic) medium-sized spiny neurons (MSNs) and the appearance of intranuclear and intracytoplasmic aggregates of mutant huntingin protein widely distributed in

neuronal and extaneuronal tissues. The clinical symptoms appear around the mid 40s manifesting in hypotonic hyperkinesias (chorea, ballism) in early stages, becoming accompanied by dystonia, pyramidal symptoms, psychosis and dementia as the disease progrediates.

Mitochondrial dysfunction in HD

The association of HD with deficient activity of mitochondrial complex II was very early revealed by a human post mortem examination [221], whereas later studies reported the involvement of complex III and IV as well [222,223]. The effect of mitochondrial dysfunction and subsequent oxidative stress to cellular compartments can be observed in the increased number of mitochondrial mutations in HD patients [224]. The inhibition of complex II either irreversibly by *3-nitropropionic acid* (3NP) [225] or reversibly by *malonate* [226] is widely applied in modeling HD *in vivo*. Systemic intoxication by 3NP has been shown to effectively recapitulate most of the clinical and histological characteristics of HD, including preferential neurodegeneration of GABAergic MSNs in the striatum [227]. Meanwhile the relevance of the malonate model as a preclinical screen has recently been questioned due to the poor reflectivity of its results to that of transgenic HD models [228].

Huntingtin protein is encoded by the IT15 (interesting transcript 15) gene localized in the short arm of chromosome 4, and the pathognomonic polyglutamine (polyQ) repeat-containing mutant variant develops due to the expansion of its CAG trinucleotid repeat sequence. The number of CAG repeats strongly correlates with clinical severity [229]. Mutant huntingtin is able to directly bind to mitochondria [230] and appears to be causative in HD due to its toxic gain of function resulting in mitochondrial dysfunction through many ways including the transcriptional repression of PGC-1α [231], the dysregulation of mitochondrial trafficking [232], and the impairment of mitochondrial Ca^{2+} handling [233] with increased susceptibility to Ca^{2+}-induced permeability transition and cytochrome *c*-mediated apoptosis [234,235]. However, an increasing amount of evidence suggests a differential effect of mutant huntingtin inclusions to cell survival, causing neurodegeneration in the form of small aggregates or aberrantly folded monomers, whilst being protective as larger aggregates probably via the sequestration of the toxic forms [236]. Furthermore, it is suggested that the relatively late symptomatic onset of an early expressing genetic mutation is due to a sort of compensatory mechanism induced by mutant huntingtin, the effect of which can be seen in the prominent resistance of young R6/2 transgenic HD animals against QUIN [237], kainic acid [238], 3NP [239] and malonate [240] compared to wild-type littermates or more aged mutants [241]. Indeed, the enhanced sensitivity of the striatum of R6/2 animals to glutamatergic exctitotoxicity appears to be age-dependent and correlates with decreased levels of glutamate transporters within the striatum [242].

Serious efforts have been made to find drug candidates capable of overcoming mitochondrial dysfunction in HD. Similarly to its results in PD, *coenzyme Q10* provides contradictory findings in HD both in preclinical and clinical levels of investigation. While a number of authors have reported significant neuroprotection by means of decrease in 3NP-induced striatal lesions [190,243] and improvement in both survival and motor performance in

transgenic HD mice [190,244], other groups investigating transgenic animal models either report amelioration only in motor performance, but not in survival [245], or find no significant differences in any endpoint [246,247]. A most interesting, recently published comprehensive study has proposed that the reported beneficial effects of coenzyme Q10 on survival and motor performance of transgenic mice could be due to inappropriate husbandry, when HD pathology could interfere with adequate nutrition and secondarily lead to coenzyme Q deficiency [247]. The first human multicenter clinical trial with Q10 (CARE-HD) showed a non-significant tendency to slow functional decline in HD [248]. Having proven its safety and tolerability in higher doses (Pre2CARE) [249], Q10 is currently running in a larger phase III study with 2.4 g/day oral administration (2CARE) along with a phase II prevention study (PREQUEL) for pre-manifest HD patients.

Likewise in PD, the antioxidant and energy buffer *creatine* has showed promising neuroprotective efficacy in animal models of HD [190,250] and has been reported to dose-dependently inhibit polyQ aggregation in a slice culture assay [251]. Furthermore, creatine-kinase has recently been proposed as a biomarker for the deterioration of HD pathology as it has been found to be reduced in 3NP-intoxicated rats [252], in transgenic HD mice and in HD patients in a disease severity-dependent manner [253]. Its oral administration has proven to be safe, tolerable, and beneficial for the antioxidant status in HD [254]. However, up to now, clinical trials with orally administered creatine have failed to reveal any improvement in the cognitive, functional and neuromuscular status of HD patients [255-257]. A phase II and a phase III clinical trial were initiated in 2007 and 2009 to evaluate tolerability and efficacy of higher doses of creatine in pre-manifest (PRECREST) and manifest (CREST-E) HD, respectively.

L-carnitine is involved in the mitochondrial exchange of fatty acids and harbors effective antioxidant properties (reviewed in [258]). It is able to suppress 3NP-induced permeability transition in isolated mitochondria [259] and has recently been found effective in a transgenic mouse model of HD [260]. A double-bind crossover study with only few participants enrolled has revealed no significant effect of acetyl-L-carnitine on clinical status of HD patients [261]. A large, randomized, double-blind, placebo-controlled clinical trial to elucidate the therapeutic potential of L-carnitine is warranted.

Cysteamine and its oxidized form *cystamine* are potent antioxidants and can exert neuroprotection via pleiotropic actions including the maintenance of antioxidant status [262-264] and the elevation of brain-derived neurotrophic factor (BDNF) secretion [265], a growth factor known to be deficient in HD-related CNS regions [266]. Both compounds have shown neuroprotective efficacy in *in vitro* [267] and *in vivo* models of HD [252,264,268,269]. It is known that the level of tissue transglutaminase enzyme is elevated in HD models *in vitro* [270], *in vivo* [268] and also in HD patients [271,272]. The long-held presumption that the ability of cystamine to inhibit transglutaminase activity [269,273] would be responsible for its neuroprotective effect has recently been challenged [274], along with the hypothesis that this enzyme would contribute to disease progression via cross-linking huntingin and promoting its aggregation [275]. Having completed a phase I dose finding and tolerability study (CYTE-I-HD) [276], a phase II clinical trial with delayed release cysteamine RP103 is ongoing.

HD patients and transgenic HD mice exhibit similar metabolic disturbances manifesting in a hypercatabolic status [277] with marked weight loss [278], which precedes

the development of motor symptoms [277] and appears to be directly related to the number of CAG repeats [279]. The involvement of impaired PGC-1α expression in the development of metabolic disturbances is assumed [280]. Dietary *n-3 polyunsaturated fatty acids* (PUFAs), such as eicosapentaenic acid (EPA), are known to improve mitochondrial metabolism in many ways, including the activation and induction of the PPAR family (PPARα, -β, -γ1, -γ2) and PGC-1α [281] besides other key transcription regulatory proteins (widely reviewed in [282]). Early and sustained treatment with PUFAs has been able to diminish behavioral alterations in R6/2 transgenic mice fundamentally [283], but the administration of ethyl-EPA to mature YAC128 transgenic mice could only result in modest but significant behavioral improvement [284]. Oral administration of PUFAs resulted in significant improvement in dyskinesias, which is the first report of a significant improvement achieved in a randomized clinical trial in HD [285]. Despite its peerless effect to prevent atrophy of the affected brain regions [286], ethyl-EPA treatment has shown no clinical benefit in a randomized, double-blind trial [287]. A multicenter, randomized trial was initiated in 2008 to re-evaluate the clinical efficacy of ethyl-EPA in HD (TREND-HD) and reported no benefit after the first six months [288].

Dysfunctional epigenetic regulation is considered to be another substantial component in the pathogenesis of HD. Accordingly, various histone deacetylase inhibitors have been found protective in animal models of HD [289,290]. *D-β-hydroxybutyrate*, a mitochondrial energizing keton body, has recently been found protective in 3NP and transgenic HD models, which effects were accompanied by the inhibition of histone deacetylation mediated by mutant huntingtin [291]. These findings indicate that D-β-hydroxybutyrate may confer neuroprotection via simultaneously targeting the mitochondrial and epigenetic alterations associated with HD, which makes this compound a valuable candidate of investigation in clinical trials to come.

HD and the kynurenine system

Early observations with exogenous [292,293] and endogenous [294,295] excitotoxins raised the suggestion that striatal excitotoxicity may take the lead in the development of HD. This hypothesis has gained support by the results of a subsequent human postmortem study revealing a massive loss of NMDAR binding in the striatum [296]. Indeed, the preferential abundance of NR2B subunit containing NMDARs on striatal neurons [297,298] and the innate hypersensitivity of their mitochondria to Ca^{2+} overload-induced permeability transition [299] along with the robust glutamatergic input of the striatum from the thalamus and the cerebral cortex [300] make this brain region a particularly vulnerable structure to glutamatergic excitotoxicity. While normal huntingtin exhibits neuroprotection against NMDA-induced neurotoxicity via binding to the scaffolding protein PSD-95, polyQ-expanded mutant huntingtin exaggerates the toxicity by inhibiting this interaction [301]. Furthermore, mutant huntingtin has been reported to increase the expression [302] and enhance the tyrosine phosphorylation of NR2B subunit-containing NMDARs [303], further contributing to the enhanced sensitivity. Very recently, the increased expression and activity of these extrasynaptic NMDARs in transgenic HD mice has been reported [304], which is associated with decreased striatal cyclic AMP response element-binding protein (CREB) signaling [304] and subsequent underexpression of PGC-1α [298]. Considering that the

enhanced sensitivity of NMDARs in HD striatum appears to be accompanied by decreased glutamate uptake in both transgenic HD mice [305] and the human HD brain [229], the demand for regulating NMDAR function makes the kynurenine system a rational target for investigation.

It has become evident very early that the intrastriatal administration of QUIN provided a fairly good model for HD [294,295,306], as it evokes cognitive, motor and neurochemical alterations closely resembling that of the human disease. It is a reasonable question whether this endogenous neurotoxin may play a role in the development of HD itself. Indeed, human studies have revealed multiple alterations in TRP metabolism in HD. On the one hand, QUIN [307] and 3-OH-L-KYN levels have been were found to be elevated in the human HD brains, particularly in the striatum [307]. Noteworthly, these alterations are apparent only in early stages of HD, and the results from studies not adjusted to the stage are fairly controversial [308,309]. Nevertheless, the role of QUIN and 3-OH-L-KYN in the initial stage of neurodegeneration in HD seems reasonable, and is in line with the observation that intrastriatally injected QUIN evokes effects that mimic earlier symptoms of HD [310]. Alterations in TRP metabolism including the abnormally high activity of the biosynthetic enzymes of QUIN and 3-OH-L-KYN have also been demonstrated in transgenic HD mice [311]. On the other hand, striatal [312], cortical [313] and cerebrospinal fluid (CSF) [309,312] KYNA levels have been reported to be decreased in HD patients, paralleled by decreased activity of the relevant KATs [312,314]. The findings that 3NP reduces KAT-I and KAT II activities in experimental rat models [209,315] indicate that the alterations of TRP metabolism might be secondary to the mitochondrial energy crisis present in HD. In such hypersensitive conditions to NMDAR-mediated toxicity, these alterations could easily contribute to the further deterioration of the neurodegenerative process. Indeed, the replication of these alterations in a KAT II knock-out mice model has demonstrated increased striatal vulnerability to QUIN [110], similarly to a transgenic HD model [316]. Correspondingly, the genetic ablation of the KAT II homologue ARO9 enhances the toxic effect of mutant huntingtin in yeasts, whereas the ablation of KMO homologue BNA4 provides protection [317]. Another research group has reported that the genetic inhibition of either KMO or tryptophan 2,3-dioxygenase (TDO) is neuroprotective in transgenic HD flies [318]. There is experimental evidence that pharmacological elevation of KYNA is neuroprotective in HD. The efficacy of the BBB-penetrant KYNA derivative prodrug 4-Cl-KYN [86] and the KMO inhibitor nicotinylalanine [107] has already been proven against striatal neurodegeneration induced by malonate [86] and QUIN [86,107] in rats, and a recently published study has demonstrated extended survival and neuroprotection in transgenic HD mice by a novel KMO inhibitor prodrug JM6 [112].

Pharmacological regulation of NMDAR activity is a double-edged sword due to its ubiquitous function in the CNS; furthermore, evidence suggests that the inhibition of synaptic NMDARs is neurotoxic via blocking BDNF and CREB pathways [38]. However, the cautious dosing of NMDAR blockers can overcome this issue and protect transgenic HD mice by the preferential blockage of extrasynaptic NMDARs [298,304]. Our laboratory has recently reported the massive neuroprotective efficacy of a novel KYNA amide N-(2-N,N-dimethylaminoethyl)-4-oxo-1H-quinoline-2-carboxamide hydrochloride [93] in N171-82Q transgenic HD mice [96], which can be a perfect candidate drug since KYNA amides may

preferentially inhibit NR2B-containing NMDARs [97], which predominate in the extrasynaptic areas. The preclinical screening of other newly synthesized KYNA amides is underway, searching for the most valuable candidates for future clinical investigations.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is also a classic, chronic, neurodegenerative disorder characterized by hippocampal, cortical and basal forebrain cholinergic neurodegeneration and atrophy with late-onset progressive dementia, which manifests in the loss of short-term and spatial memory and eventually most of the cortical functions. The process is accompanied by the formation of predominantly extracellular plaques of β-amyloid (Aβ) and predominantly intracellular deposits of neurofibrillary tangles (NFTs) constituted by hyperphosphorylated tau proteins (pTau). AD is the most common cause of dementia (50–60%), affecting approximately 30% of the elderly in the developed world. AD is typically a sporadic disease; familial forms are very rare and are characterized by presenile onset (reviewed in [319]).

Mitochondrial dysfunction in AD

A significant decrease in the activity of mitochondrial complex IV in the affected regions of human AD brains has been reported by post-mortem studies [320,321], indicating the contribution of energy impairment in the underlying pathology. In addition, AD patients appear to harbor numerous mtDNA mutations, which can severely impair mitochondrial transcription [322]. The dysregulation of mitochondrial dynamics in AD neurons has also been reported [323]. Both extracellular and intracellular Aβ are known to contribute to neurotoxicity, the most toxic forms are small soluble globular structures (reviewed in [324]). Among experimental conditions, Aβ preferentially accumulates in the mitochondria [325], where it is able to inhibit the activity of complex IV [326] and promote mtPTP formation [327]. The preferential ability of oligomeric Aβ to accumulate in the mitochondria is supposed to be partly due to its increased lipid permeability (reviewed in [328]); however, a selective transport mechanism by the translocase of the outer membrane (TOM) machinery [329] and intramitochondrial Aβ production have also been reported [330]. Additionally to the indirect elevation of ROS production through disrupted respiration, Aβ fragments *per se* generate free radicals [331]. The co-localization of the dense core plaques with the fluorescent signaling of free radicals well demonstrates the direct connection between Aβ and ROS [332]. The massive overproduction of ROS can increase the accumulation of Aβ *vice versa*, completing a vicious circle [331]. The level of intramitochondrial Aβ correlates with the extent of mitochondrial dysfunction and severity of cognitive impairment in transgenic AD mice [333]. Synaptosomes preferentially accumulate Aβ, and show increased sensitivity to Aβ-toxicity [334]. Recently, the crucial role of the amyloid β-binding alcohol dehydrogenase (ABAD) enzyme has been revealed as a potential direct molecular link between Aβ and mitochondrial pathologies [335], which includes the selective inhibition of complex IV, ROS generation, mitochondrial transition [336] and the inhibition of intramitochondrial Aβ degrading presequence peptidase (PreP) [337]. Aβ has also been shown to directly interact with cyclophilin D (CypD) and adenine nucleotide translocase (ANT) [338] hence promoting the assembly of mtPTP. Most recently, Aβ has been reported to disintegrate the anterograde

transport of synaptosomes, leading to the degeneration of the synapses [339]. Besides, amyloid precursor protein (APP) [340] and $A\beta_{25-35}$ [341] inhibit the entry of nuclear encoded proteins including subunits essential for the correct assembly of respiratory complexes, which triggers further deterioration in mitochondrial function and more extensive ROS production. Intracellular Aβ severely affects the function of the proteasomal degradation system as well. This effect is exaggerated in the absence of parkin [342], which appears to promote the clearance of toxic $A\beta_{1-42}$ [343]. Aβ can indirectly trigger the hyperphosphorylation of tau through the activation of glycogen synthase kinase-3beta (GSK-3β) and mitogen activated protein kinase (MAPK) [344,345], which results in the disintegration of axonal structure. Recent studies tend to support earlier observations [346,347] that the amount of Aβ and pTau burden within the brain is in direct correlation with the severity of cognitive impairment [348-351], whereas plasma and CSF levels of Aβ have an inverse correlation [352-354]. The direct contribution of pTau to mitochondrial dysfunction has also been reported as P301L tau transgenic mice exhibit a decreased activity of complex I and decreased expression of complex V [355,356]. The involvement of the deregulation of metabolic master regulator and mitochondrial biogenesis enhancer PGC-1α has recently been demonstrated in AD pathology as well, as its expression is decreased in the hippocampus of AD patients [357].

Epidemiological studies indicate that the regular intake of dietary *3-n PUFAs* is associated with a decreased risk for AD [358]. 3-n PUFAs are involved in several mitochondrial processes such as gene expression, free radical production, mitochondrial apoptosis and calcium homeostasis (reviewed in [359]). The plasma level of the 3-n PUFA docosohexaenaic acid (DHA) – an essential neuronal membrane phospholipid component – has been reported to inversely correlate with the severity of cognitive decline in AD [360]. Accordingly, experimental depletion of 3-n PUFA causes behavioral alterations, evokes a marked loss in postsynaptic proteins [361] and in NMDAR subunits NR2A and NR2B, and triggers the activation of apoptotic caspases [362] in transgenic AD models. These effects can be prevented by the dietary administration of DHA. DHA has also been demonstrated to reduce amyloid burden and tau phosphorylation [363,364] and to improve cognition in transgenic AD mice [364]. These protective effects of DHA are proposed to be mediated by the elevation of ApoE receptor family member SorLa (LR11) [365], which is robustly downregulated in AD [366] and appears to be essential in the regulation of APP trafficking and intracellular Aβ accumulation [367]. Initial clinical trials with 3-n PUFA/DHA supplementation could only detect significant cognitive improvement in patients with mild cognitive impairment (MCI) [368,369] or with very mild cognitive dysfunction [370], but not with definitive AD. A subsequent clinical trial has also failed to show any cognitive benefit in AD [371]; however, subgroup analyses have revealed significantly lower declines in Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and Mini-Mental State Examination (MMSE) scores during the 18 months of investigation among ApoE4 non-carrier patients, an allele which has been associated with increased risk for AD when present [372]. A phase I/II (NCT01058941) and a phase III clinical trial (MAPT) are currently ongoing to study the potential therapeutic efficacy of DHA through different lengths of observation period.

Acetyl-L-carnitine has widely been tested in AD as well. *In vitro* and *in vivo* studies indicate that this compound could be of therapeutic use in AD since it potently reduces oxidative damage [373,374], restores metabolic changes [375], attenuates tau phosphorylation [376], protects against Aβ toxicity [373], and halts cognitive decline [374,376] in a wide range of AD models. Human trials from the early 1990s provided promising results with significantly slower rate of cognitive deterioration in many aspects [377-379]. A subsequent larger trial have failed to demonstrate any significant improvement [380]; however, there has been an observable tendency to slow the rapid deterioration of relatively younger patients with early-onset AD, which has proved to be statistically significant during the reanalysis of the data [381]. Unfortunately, in a subsequent prospective study acetyl-L-carnitine has failed to halt the decline in patients with young-onset AD [382]. Some recent results still seems to give hope, demonstrating that acetyl-L-carnitine improves the response rate of AD patients to acetylcholinesterase (AChE) inhibitor therapy [383], which is currently the first-line treatment in AD. Two recent clinical investigations run by the same research group have reported clinically observable improvement and maintenance in performance in many outcomes due to the administration of an antioxidant combination formula containing 500 mg acetyl-L-carnitine [384,385]. An independent phase II clinical trial with MCI patients has just been finished (NCT00903695), while another phase II study with MCI and definitive AD patients (NCT01320527) is currently recruiting participants to confirm or deny the promising results of this formulation.

One of the biggest disappointments was the failure of a former non-selective anti-histamine 2,8-dimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole hydrochloride (*latrepirdine, Dimebon*). Latrepirdine has provided neuroprotection and enhanced cognitive performance in a wide range of experimental models [386-388]. It is presumed to have multiple mechanisms of action that might include NMDAR inhibition [389], AchE inhibition [390], enhancement of cerebral glucose utilization [391] and the improvement of mitochondrial function [388], mediated partly by the inhibition of L-type Ca^{2+} channels [386]. However, its efficacy to inhibit mtPTP [392] has recently been questioned [393] along with the clinical relevance of its ability to block NMDARs and AChE [387]. The initial human investigations have demonstrated unusually promising results with a phase II clinical trial (NCT00377715) reporting significant improvement in all primary and secondary outcomes [394]. In contrast, the results of a phase III efficacy and safety study (CONNECTION) have recently been announced reporting zero benefit in any endpoint [395]. Several phase III trials with latrepirdine have subsequently been terminated (CONTACT, NCT00912288, NCT00939783), one has just been completed (NCT00838110) and another one is still ongoing to elucidate its efficacy in AD patients on Donepezil treatment (CONCERT). It might be possible that the apparent ability of latrepirdine to increase cognitive performance is achieved through mechanisms not necessarily involved in the pathology of AD, which is in line with the recent findings that this efficacy of latrepirdine is unrelated to cerebral Aβ burden in transgenic AD mice [396], but it is also apparent in healthy animals [396,397]. The robust discrepancies between preclinical and clinical examinations, and also between two independent clinical trials raise serious concerns about the correct interpretation of preclinical findings.

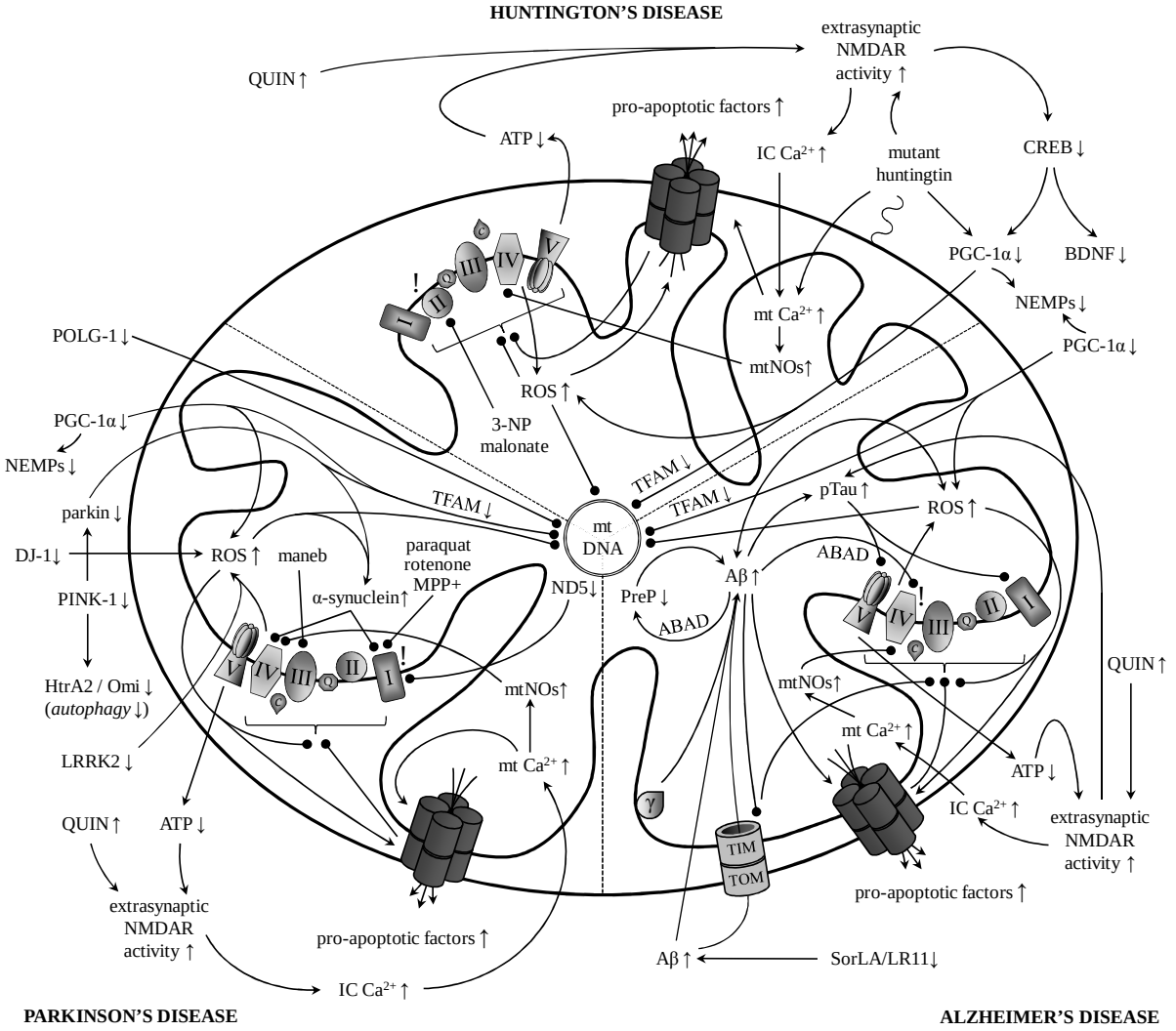
AD and the kynurenine system

The distribution of the pathological hallmarks of AD in the brain is consistent with the regions of memory formation, where the glutamatergic circuitry is fundamental. One of the most affected structures is the hippocampal formation. Hippocampus, and particularly cornu ammonis 1 (CA1) [398], is known to be extremely vulnerable to a wide range of insults including glutamatergic excitotoxicity (reviewed in [399]), at least in part due to the high concentration of exctitatory amino acid receptors. Experimental AD models provide evidence that the presence of $A\beta_{1-42}$ further increases neuronal vulnerability to excitotoxic stress [400,401]. Furthermore, $A\beta_{1-42}$, but not $A\beta_{1-40}$, significantly induces the expression of indoleamine 2,3-dioxygenase 1 (IDO1) and the production of QUIN [402], which are both abundantly present in AD hippocampus with the highest abundance in the perimeter Aβ senile plaques [403] and in specific conjunction with NFTs [404]. The increased production of QUIN in AD brain has been associated with the need for inflammatory circumstances being present [405,406], which is in line with the recent findings that $A\beta_{1-42}$ pre-treatment primes only a slight induction of IDO expression in *in vitro* microglia models, and the robust activation can only be seen after the administration of the pro-inflammatory cytokine interferon-γ to the $A\beta_{1-42}$ pre-treated cells [407]. QUIN has a high affinity towards inducing lipid peroxidation [408], which corresponds with the observations that lipid peroxidation is a characteristic feature of AD but not of normal aging (reviewed in [409]). There is considerable evidence that QUIN also contributes to the hyperphosphorylation of tau proteins via the overactivation of NMDARs [410]. These findings substantially overwrite the conclusions from earlier observations that QUIN would not play a crucial role in the development of neurodegeneration in AD.

The findings regarding KYNA are not that concording. Although decreased KYNA levels were found in the blood [411] and CSF [309] of AD patients, marked elevation in KYNA concentrations was detected in the striatum with increased KAT I and KAT II activities, and also slight elevation in the hippocampus with no KAT alterations [412]. The elevation of KYNA might be due compensatory mechanisms and can contribute to the cognitive impairment [413-415] as it is suggested also in Down syndrome and schizophrenia.

There is considerable evidence that the modulation of QUIN synthesis can offer neuroprotection in animal models of AD. Recently the novel KMO inhibitor prodrug JM6 has been reported to be effective in preventing spatial memory deficits, anxiety behavior, and synaptic loss in transgenic AD mice [112]. In experimental conditions, the systemic administration of probenecid with L-KYN as an immediate metabolic precursor of KYNA exerts neuroprotection against intrahippocampal $A\beta_{25-35}$ [102]. Similar effects have been reported about 4-Cl-KYN against QUIN induced hippocampal toxicity [87]. However, the therapeutic relevance of these approaches in AD might be questioned with respect to the arising evidence that elevated KYNA levels are involved in the cognitive decline in AD. It seems reasonable that the treatment of AD via the modulation of TRP metabolism will require the most sophisticated pharmaceutical approache that includes, on the one hand, the inhibition of QUIN synthesis to provide neuroprotection against excitotoxic insults, and on the other hand, the reduction of excessive KYNA levels to offer proper NMDAR function for adequate memory formation and recall [414,415].

Figure 3. Mitochondria in neurodegenerative diseases



The figure presents the schematic overview of the processes involved in mitochondrial dysfunction related to Parkinson's, Huntington's and Alzheimer's diseases. For detailed description, we refer to the corresponding parts of the article.

↑ = increased presence/expression/activity; ↓ = decreased presence/expression/activity; arrow = promotion; bulb-headed arrow = inhibition/deterioration; I-V = mitochondrial complexes; 3NP = 3-nitropropionic acid; Aβ = β-amyloid (toxic isoforms); ABAD = amyloid β-binding alcohol dehydrogenase; BDNF = brain-derived neurotrophic factor; c = cytochrome *c*; CREB = cyclic AMP response element-binding protein; γ = gamma secretase; HtrA2/Omi = high temperature requirement factor A2; IC Ca^{2+}= intracellular calcium; LRRK2 = leucine-rich repeat kinase 2; MPP+ = 1-methyl-4-phenylpyridinium; mt Ca^{2+}= mitochondrial calcium; mtDNA = mitochondrial DNA; mtNOS = mitochondrial nitric oxide synthase; NEMP = nuclear-encoded mitochondrial protein; NMDAR = *N*-methyl-D-aspartate-sensitive glutamate

receptor; PINK1 = (PTEN)-induced putative kinase 1; PGC-1α = PPARγ coactivator-1α; POLG1 = mtDNA polymerase gamma 1; PreP = presequence peptidase; pTau = hyperphosphorylated tau protein; Q = coenzyme Q10 (ubiquinone); QUIN = quinolinic acid; ROS = reactive oxygen species; TFAM = mitochondrial transcription factor A; TIM = translocase of the inner membrane; TOM = translocase of the outer membrane.

CONCLUDING REMARKS

The pathogenesis of common neurodegenerative disorders such as PD, HD and AD is robustly associated with mitochondrial dysfunction. The putative origins of these diseases are distinct; however, the shared contribution of mitochondrial dysfunction can lead to certain extent of symptomatic overlap in the terminal phases of the clinical pathology. The underlying causes behind the preferential involvement of particular CNS regions in these diseases require further elucidation; however, it can be concluded that the extreme energy demand of the affected structures make them highly vulnerable to any sort of mitochondrial disturbances. Mitochondria targeted therapies aiming to overcome the energy impairment and the extensive oxidative stress show great promises in a wide range of experimental conditions. Unfortunately, the results gained from human clinical trails are rather disappointing or at best very controversial. One of the reasons underlying this phenomenon can be the extreme genetic and conditional homogeneity of the experimental animals in contrast to the heterogeneity of the clinical population usually recruited in a trial. Another concern is the relatively young age of animals applied for the experimental setups versus the relatively aged subjects of the clinical trials. This can lead to false positive results in terms of neuroprotection *in vivo*, since younger animals can be more resistant to the experimentally induced mitochondrial toxicity, thus the protective effect of a drug candidate can be more pronounced. Thirdly, most of the preclinical investigations focus on the prevention or reduction of the neurodegenerative effect of the applied toxin or genetic alteration, which is obviously unable to model the status of trial participants, who have already suffered an extensive loss of neurons in the affected CNS regions by the time of the diagnosis. These shortcomings are to be considered in the future during the setup of both *in vivo* examinations and human trials.

Considering that NMDAR-mediated excitotixicity seems to be ubiquitous in neurodegenerative disorders, and that the affected structures possess anatomical and physiological susceptibility to be highly sensitive to this process, the investigation of the kynurenine system as the endogenous regulator of NMDAR functioning is of great interest. May the alterations in TRP metabolism be rather secondary to the underlying pathological processes, it can be concluded that the local decrease in KYNA and the local elevation in QUIN and 3-OH-L-KYN levels can contribute to neurodegeneration through the overactivation of NMDARs. Alzheimer's disease might be an exception where the elevation of KYNA levels in the affected structures has been reported, which probably contributes to the development of cognitive decline. Promising experimental results have come to rise in the near past in different models of neurodegenerative diseases through the exogenous regulation of TRP metabolism. The application of novel KYNA analogues and KMO inhibitors show the greatest therapeutic promise. Thorough examinations and well set-up human trials are warranted to elucidate the therapeutic potential of these candidates.

LIST OF ABBREVIATIONS

3-HAO = 3-hydroxyanthranic acid 3,4-dioxygenase; 3NP = 3-nitropropionic acid; 3-OH-ANA = 3-hydroxy-anthranilic acid; 3-OH-L-KYN = 3-hydroxy-L-kynurenine; ; Aβ = β-amyloid ; ABAD = amyloid β-binding alcohol dehydrogenase; AChE = acetylcholinesterase; AD = Alzheimer's disease; ADAS-cog = Alzheimer's Disease Assessment Scale cognitive subscale; AIF = apoptosis-inducing factor; ANA = anthranilic acid, ANT = adenine nucleotide translocase; Apaf-1 = apoptotic protease activating factor 1; APP = amyloid precursor protein; BBB = blood–brain barrier; BDNF = brain-derived neurotrophic factor; CA1 = cornu ammonis 1; CREB = cyclic AMP response element-binding protein; CSF = cerebrospinal fluid; CypD = cyclophilin D; DHA = docosohexaenaic acid; EPA = eicosapentaenic acid; GABA = γ-aminobutyric acid; GSK-3β = glycogen synthase kinase-3beta; H_2O_2 = hydrogen peroxide; HD = Huntington's disease; HtrA2 = high temperature requirement factor A2 (Omi); IDO = indoleamine 2,3-dioxygenase; IT15 = interesting transcript 15; JM6 = 2-(3,4-dimethoxybenzenesulfonylamino)-4-(3-nitrophenyl)-5-(piperidin-1-yl)methylthiazole; KAT = kynurenine aminotransferase; KMO = kynurenine 3-monooxygenase (kynurenine 3-hydroxylase); KYNA = kynurenic acid; latrepirdine = 2,8-dimethyl-5-(2-(6-methylpyridin-3-yl)ethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole hydrochloride; L-KYN = L-kynurenine; LRRK2 = leucine-rich repeat kinase 2; MAPK = mitogen activated protein kinase; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MnSOD = manganese superoxide dismutase; MPP+ = 1-methyl-4-phenylpyridinium; MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSN = medium-sized spiny neuron; mtAAT = aspartate aminotransferase; mtDNA = mitochondrial DNA; mtNOS = mitochondrial nitric oxide synthase; mtPTP = mitochondrial permeability transition pore; NCR-631 = 4,6-dibromo-3-OH-ANA; nDNA = nuclear DNA; NFT = neurofibrillary tangle; NMDA = *N*-methyl-D-aspartate; NMDAR = *N*-methyl-D-aspartate-sensitive glutamate receptor; nNOS = neuronal nitric oxide synthase; $NO^{\bullet}$ = nitric oxide radical; NOS = nitric oxide synthase; $O_2^{-\bullet}$ = superoxide anion; $OH^{-\bullet}$ = hydroxyl radical; PARP-1 = poly(ADP-ribose) polymerase-1; PD = Parkinson's disease; PGC-1α = PPARγ coactivator-1α; PINK1 = (PTEN)-induced putative kinase 1; PNU 156561 = 4,5-dichlorobenzoylalanine (FCE 288833A); POLG1 = mtDNA polymerase gamma 1; polyQ = polyglutamine; PPARγ = peroxisome proliferator-activated receptor-γ; PreP = presequence peptidase; PSD-95 = postsynaptic density protein of molecular weight 95 kDa; pTau = hyperphosphorylated tau protein; PUFA = polyunsaturated fatty acid; QUIN = quinolinic acid; Ro 61-8048 = 3,4-dimethoxy-[-N-4-(nitrophenyl)thiazol-2-yl]-benzenesulfonamide; ROS = reactive oxygen species; SNP = single nucleotide polymorphism; SNpc = substantia nigra pars compacta; TFAM = mitochondrial transcription factor A; TIM = translocase of the inner membrane; TOM = translocase of the outer membrane; TRAP1 = tumor necrosis factor receptor-associated protein 1; TRP = tryptophan; UPF 648 = (1S,2S)-2-(3,4-dichlorobenzoyl)-cyclopropane-1-carboxylic acid.

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CONFLICTS OF INTEREST

Authors report no relevant conflicts of interest.

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